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Differences in anticoagulation strategy and outcome in atrial fibrillation patients with chronic kidney disease: a CODE-AF registry study

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Abstract

Purpose: Dose reduction of non-vitamin K antagonist oral anticoagulants (NOACs) is indicated in patients with atrial fibrillation (AF) with renal impairment. This study investigated anticoagulation patterns and outcomes in patients with chronic kidney disease (CKD).

Materials and methods: In a prospective observational registry (CODE-AF), 3445 patients with non-valvular AF including 1129 with CKD (estimated glomerular filtration rate ≤ 60 mL min^{-1} 1.73 m^{-2}) were identified between June 1, 2016, and July 3, 2017.

Results: Compared with patients with no-CKD, patients with CKD more frequently had a high stroke risk (94.9% vs. 67.0%, $p < 0.001$) and higher NOAC usage rate (61.1% vs. 47.8%, $p < 0.001$). Among 718 patients with renal indication for dose reduction (RIDR), 7.5% were potentially overdosed. Among 2587 patients with no-RIDR, 79% were potentially underdosed. Compared with patients with no-RIDR, the underdose rates of dabigatran (0% vs. 88.6%, $p = 0.001$) and rivaroxaban (0% vs. 79.5%, $p = 0.001$) were lower in patients with RIDR. However, the underdose rate of apixaban was not different (62.5% vs. 53.9%, $p = 0.089$). The overdose rate of dabigatran (7.5% vs. 0%) and rivaroxaban (13.7% vs. 0%) was higher in RIDR than in no-RIDR patients. Stroke/transient ischemic attack was significantly higher in CKD patients (1.4 vs. 0.6 per 100 person-years, $p = 0.045$). Aspirin significantly increased minor bleeding in CKD patients compared with controls ($p = 0.037$).

Conclusion: CKD patients might have a high stroke risk and NOAC usage rate. The underdose rate of NOACs decreased in CKD patients, except for apixaban. Aspirin significantly increased minor bleeding in CKD patients.

Keywords: Atrial fibrillation, Anticoagulation, Kidney diseases, Stroke

Introduction

Atrial fibrillation (AF) is the most common, sustained cardiac arrhythmia occurring in 1–2% of the general population [1], and is associated with increased morbidity and mortality [2, 3]. Because AF increases with advancing age, AF is becoming a significant public health burden in Asia, including Korea, as the aging population

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rapidly increases. AF is associated with a fivefold increase in stroke risk, and one in five cases of stroke is attributed to this arrhythmia [4]. AF is present in 15–20% of patients with chronic kidney disease (CKD) [5]. Abnormal renal function is related to an increased rate of bleeding [6, 7].

The net clinical benefit of oral anticoagulant (OAC) treatment is almost universal, with the exception of patients with a very low stroke risk; therefore, OAC should be used in most patients with AF [8, 9]. Compared with warfarin, non-vitamin K antagonist OACs (NOACs) are more convenient to use and demonstrated at least equivalent efficacy, with less intracranial bleeding, in pivotal clinical trials [10]. However, all NOACs have some degree of renal clearance (80% for dabigatran, 50% for edoxaban, 35% for rivaroxaban, and 27% for apixaban), and dose reduction is indicated in patients with clinically significant renal impairment [11, 12]. Failure to reduce the dose in patients with severe renal disease may increase the risk of bleeding, whereas inappropriate dose reduction without a firm indication may decrease the effectiveness of stroke prevention.

Although most patients with non-valvular AF benefit from anticoagulation to prevent ischemic stroke and systemic embolism, those with renal dysfunction face high risks of both thromboembolism and bleeding during antithrombotic therapy [6, 7]. In observational studies, anticoagulant therapy is frequently not administered in patients with AF and renal dysfunction [13, 14] owing to the concern that bleeding may outweigh the potential benefit. A key question is whether reliable anticoagulation without the risk of excessive bleeding can be achieved in patients with reduced renal function. Therefore, the goal of the present study was to investigate the patterns of anticoagulation. Specifically, we examined the use and outcomes of various OAC strategies.

Subjects and methods

Study design and centers

The study design of the CODE-AF (COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation) was described in a previous study [15]. Briefly, CODE-AF is a prospective, multicenter, observational study performed in patients with AF aged > 18 years and attending any of 10 tertiary centers, encompassing all geographical regions of Korea. The study enrollment period started on June 2016 and will end on October 2018. The primary objective of CODE-AF, by generating a prospective multicenter AF registry, is to evaluate the outcome of medical managements such as anticoagulation, rate control, and rhythm control treatments. The registry was designed and coordinated by the Korea Heart Rhythm Society, which provides support to related committees, national coordinators, and participating centers. Data are entered in a common electronic database that limits inconsistencies and errors and provides online help for key variables. Each center has access to its own data and data from all other participating centers. The study was approved by the ethics committee of each center, and all patients provided informed consent for their inclusion. This study was registered at ClinicalTrials.gov (NCT02786095).

Patients

From June 1, 2016, to July 3, 2017, a total of 6966 patients with non-valvular AF were enrolled in the CODE-AF registry. The following were the exclusion criteria: (1) low or intermediate stroke risk ($n = 1831$), (2) high stroke risk without anticoagulation ($n = 820$), (3) valvular heart disease ($n = 34$), and (4) < 6-month follow-up ($n = 836$). Finally, a total of 3445 non-valvular AF patients taking OACs, including 1129 patients with CKD, were enrolled in this study (Fig. 1).

Data collection was performed according to the same criteria and was usually carried out by personnel with no clinical activity assigned to the project. A follow-up visit was scheduled every 6 months, either through personal interview or telephone contact (data not shown).

Renal function and indication for dose reduction

Chronic kidney disease (CKD) is defined by Kidney Disease Improving Global Outcomes as a reduction in renal function with a reduction in glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 for 3 months or longer or with the presence of albuminuria [16]. The most recent serum creatinine levels within 1 year before treatment initiation were abstracted. We calculated the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease

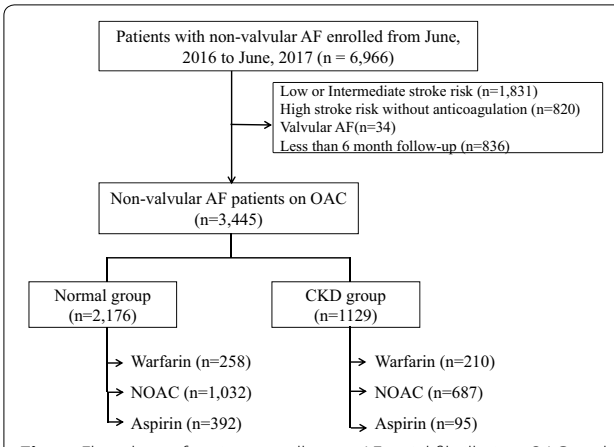

Fig. 1 Flowchart of patient enrollment. AF, atrial fibrillation; OAC, oral anticoagulant; CKD, chronic kidney disease; NOAC, non-vitamin K antagonist oral anticoagulant

Epidemiology Collaboration equation [17]. Patients were considered to have a renal indication for dose reduction (RIDR) if they were prescribed with dabigatran and had an eGFR of < 50 mL min^{-1} 1.73 m^{-2}, prescribed with rivaroxaban, and had eGFR < 50 mL min^{-1} 1.73 m^{-2}. The indication for dose reduction with apixaban (per the approved product label) is more complex than our criteria and requires two of the following three criteria: age ≥ 80 years, weight ≤ 60 kg, and serum creatinine level ≥ 1.5 mg/dL.

We considered drug interactions with P-glycoprotein and cytochrome P450 3A4 inhibitors based on European Heart Rhythm Association guidelines [18]. We did not include the use of these medications in the criteria for dose reduction because they are generally considered relative indications, and the effects on the NOAC plasma levels vary substantially among patients and drugs. The most commonly used interacting medications in this cohort were diltiazem, amiodarone, dronedarone, and verapamil; we included the use of these medications as matching variables in propensity score models and conducted subgroup analyses according to drug interactions.

Guidelines recommend estimating the stroke risk in patients with AF based on the CHA_2DS_2-VASc score (Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥ 75 years [doubled], Diabetes, Stroke [doubled]–Vascular disease, Age 65–74 years, and Sex category [female] score) [19, 20]. In general, patients without clinical stroke risk factors or with a low risk (CHA_2DS_2-VASc 0 or 1 [female]) do not need antithrombotic therapy, whereas patients with high stroke risk factors (i.e., CHA_2DS_2-VASc ≥ 2) should be treated with OAC [19, 20].

Outcomes

The primary efficacy end point was the composite of all stroke (both ischemic and hemorrhagic) and systemic embolism. Secondary end points included the composite of stroke, non-central nervous system systemic embolism, cardiovascular death, and myocardial infarction, and the individual components of the composite end points. The principal safety end point was the composite of major and non-major clinically relevant bleeding events [21]. Bleeding events involving the central nervous system that met the definition of stroke were adjudicated as hemorrhagic strokes and included in both the primary efficacy and safety end points. An independent clinical events committee applied the protocol definitions and adjudicated all suspected stroke, systemic embolism, myocardial infarction, death, and bleeding events contributing to the prespecified efficacy and safety end points.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables were reported as frequencies (percentage). Statistical analyses were performed with SPSS 21.0 statistical software (SPSS Inc., Chicago, IL, USA). All p values were two-tailed, and values < 0.05 were considered statistically significant.

Results

Baseline characteristics

Among 1129 patients with CKD, the median age was 75.0 years (interquartile range [IQR]: 71.0–80.0 years), the median GFR was 44.5 mL min^{-1} 1.73 m^{-2} (IQR: 39.0–54.0 mL min^{-1} 1.73 m^{-2}), the median CHA_2DS_2-VASc score was 3.7 (IQR: 3.0–5.0), and the median HAS-BLED score was 2.4 (IQR: 2.0–3.0). Patients were followed up for a median of 10.7 months (IQR: 9.5–12.3 months). In the 2176 patients without CKD (no-CKD), the median age was 63.7 years (IQR: 58.0–71.0 years), the median eGFR was 85.5 mL min^{-1} 1.73 m^{-2} (IQR: 69.5–95.1 mL min^{-1} 1.73 m^{-2}), the median CHA_2DS_2-VASc was 2.3 (IQR: 1.0–3.0), and the median HAS-BLED score was 1.7 (IQR: 1.0–2.0) (Table 1). Patients were followed up for a median of 10.5 months (IQR: 9.5–12.3 months).

Figure 2 shows the comparison of stroke risk and stroke prevention between CKD and no-CKD patients with AF. Compared with no-CKD patients, CKD patients more frequently had a high stroke risk (94.9% vs. 67.0%, $p < 0.001$) and a higher usage rate of NOAC (61.1% vs. 47.8%, $p < 0.001$). Among the NOACs, apixaban was most frequently used in CKD patients than in controls (32.6% vs. 18.4, $p = 0.001$).

Dosage pattern of NOACs in CKD patients

Figure 3 shows the comparison of the dosage patterns of NOACs between CKD and no-CKD patients. The overall underdose rate of NOACs was 56.8% and 49.8% in the no-CKD and CKD groups, respectively ($p = 0.04$). In the CKD group, overuse rate of NOACs was observed in 2.9% of patients. Compared with no-CKD patients, CKD patients had lower underdose rates of dabigatran (47.9% vs. 63.0%, $p = 0.002$) and rivaroxaban (35.4% vs. 62.8%, $p = 0.001$). However, CKD patients had a higher underdose rate (57.1% vs. 46.4%, $p = 0.003$) and a lower optimal dose rate of apixaban (42.7% vs. 53.4%, $p = 0.003$).

Among the 718 patients with RIDR, 7.5% were potentially overdosed. Among the 2587 patients with no-RIDR, 79% were potentially underdosed. Compared with patients with no-RIDR, the underdose rates of dabigatran (0% vs. 88.6%, $p = 0.001$) and rivaroxaban (0% vs. 79.5%, $p = 0.001$) were lower in patients with RIDR. However, the underdose rate of apixaban was

Table 1 Baseline characteristics of patients

	Normal ($n=2176$)	CKD ($n=1129$)	p value
Female, *n*	709 (32.6)	535 (47.4)	0.001
Age, years	63.7 (58.0–71.0)	75.0 (71.0–80.0)	0.001
Weight, kg	69.8 ± 11.0	59.7 ± 10.0	0.001
BMI, kg/m^2	25.4 ± 3.2	23.2 ± 3.2	0.001
eGFR, mL min^{-1} 1.73 m^{-2}	85.5 (69.5–95.1)	44.5 (39.0–54.0)	0.001
Paroxysmal AF	1463 (67.2)	722 (64.0)	0.067
Persistent AF	612 (28.1)	346 (30.6)	0.067
Permanent AF	101 (4.6)	61 (5.4)	0.067
CHA_2DS_2-VASc score	2.3 (1.0–3.0)	3.7 (3.0–5.0)	0.001
HAS-BLED score	1.7 (1.0–2.0)	2.4 (2.0–3.0)	0.001
Heart failure	186 (8.5)	188 (16.7)	0.001
Hypertension	1407 (64.7)	863 (76.4)	0.001
Diabetes mellitus	516 (23.7)	378 (33.5)	0.001
Stroke/TIA	309 (14.3)	250 (22.2)	0.001
Myocardial infarction	76 (3.5)	55 (4.9)	0.054
PAD	98 (4.5)	77 (6.8)	0.009
History of bleeding	217 (10.0)	155 (13.7)	0.43
ICD insertion	27 (1.2)	16 (1.4)	0.671
Pacemaker insertion	98 (4.5)	128 (11.3)	0.001
Dyslipidemia	743 (34.1)	404 (35.8)	0.348
Cancer	203 (9.3)	130 (11.5)	0.048
LA volume, mL/m^2	53.9 ± 29.0	68.4 ± 40.4	0.001
LVEF, %	60.2 ± 20.2	58.6 ± 9.6	0.149
Follow-up duration, months	10.5 (9.5–12.3)	10.7 (9.5–12.3)	0.051

Data are presented as mean ± standard deviation or number (percentage)

AF, atrial fibrillation; BMI, body mass index; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age 75 years or older, Diabetes mellitus, previous Stroke/transient ischemic attack, Vascular disease, Age 65 to 74 years, Sex category (female); CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; ICD, implantable cardioverter defibrillator; LA, left atrial; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; TIA, transient ischemic attack

not different (62.5% vs. 53.9%, $p=0.089$). The overdose rates of dabigatran (7.5% vs. 0%) and rivaroxaban (13.7% vs. 0%) were higher in the RIDR group than in the no-RIDR group. In contrast, the overdose rate of apixaban was lower in the RIDR group than in the no-RIDR group (Fig. 4).

The NOAC usage patterns according to eGFR are presented in Fig. 5. Compared with patients with eGFR ≥ 50 mL min^{-1} 1.73 m^{-2}, the underdose rates of dabigatran and rivaroxaban were significantly lower in both the eGFR 30–50 mL min^{-1} 1.73 m^{-2} and < 30 mL min^{-1} 1.73 m^{-2} groups; however, the underdose rate of apixaban was lower only in patients with eGFR < 30 mL min^{-1} 1.73 m^{-2}.

Adverse event rate in CKD patients

Figure 6 shows the comparison of adverse outcome between no-CKD and CKD patients. The stroke/transient ischemic attack event rate was 0.6 and 1.4 per 100 person-years in the no-CKD and CKD groups, respectively. Stroke/transient ischemic attack was significant higher in CKD patients than in no-CKD patients ($p=0.045$). And the most of stroke occurred earlier after NOAC prescription. In total, 29% occurred within 6 months, and 71% occurred within 7 months. The event rate for major bleeding was 0.5 and 0.2 per 100 person-years in the no-CKD and CKD groups, respectively. There was no statistically significant difference in the event rate of major bleeding.

The outcomes according to different OAC strategies are presented in Fig. 7. The incidence of stroke/transient ischemic attack with warfarin usage was 2.2 and 0.6 per 100 person-years in the no-CKD and CKD groups, respectively ($p=0.336$). Aspirin increased minor bleeding in the CKD group compared with the normal group (5.6 vs. 2.0 per 100 person-years, $p=0.037$).

Discussion

Main findings

The main findings of this study were that CKD patients had a higher stroke risk and usage rate of NOAC than patients with no-CKD. Second, the underdose rates of dabigatran and rivaroxaban were lower in CKD patients, except for apixaban. The overdose rate was higher in CKD patients, also except for apixaban. Third, stroke/transient ischemic attack was significantly higher in CKD patients than in no-CKD patients. In particular, warfarin significantly increased stroke/transient ischemic attack in CKD patients. Aspirin significantly increased minor bleeding in CKD patients.

High stroke risk of CKD

The definition of CKD in most AF trials is relatively strict. Although an estimated creatinine clearance rate of < 60 mL/min is indicative of CKD, a number of trials in AF patients have used creatinine clearance < 50 mL/min to adapt NOAC dosage, usually estimated using the Cockroft–Gault formula. The creatinine clearance in AF patients can deteriorate over time [22].

Among patients with AF, renal dysfunction is common and progressively increases with older age [23]. As reflected in the CODE-AF trial, such patients also demonstrate complex comorbidities, including congestive heart failure, prior hypertension, and diabetes.

Consistent with prior observations, this study demonstrates that patients with renal dysfunction are at

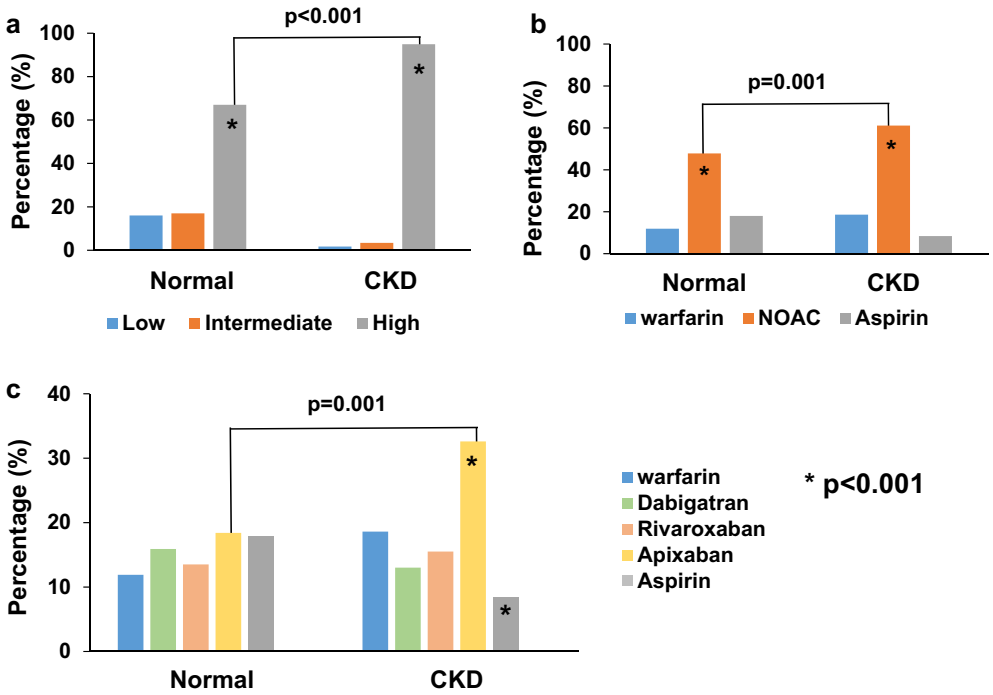

Fig. 2 Stroke risk and stroke prevention in atrial fibrillation patients with CKD. **a** Comparison of stroke risk in each group. The proportion of high stroke risk was higher in the CKD group than in the normal group (94.9% vs. 67.0%, $p < 0.001$). **b** Comparison of oral anticoagulant medication in each group. The CKD group had a higher usage rate of NOAC than the normal group (61.1% vs. 47.8%, $p = 0.001$). **c** Comparison of NOAC in each group. Among NOACs, apixaban was most frequently used in CKD patients compared with controls (32.6% vs. 18.4, $p = 0.001$). CKD, chronic kidney disease; NOAC, non-vitamin K oral anticoagulant. Asterisks indicate that the percentage was different between the groups

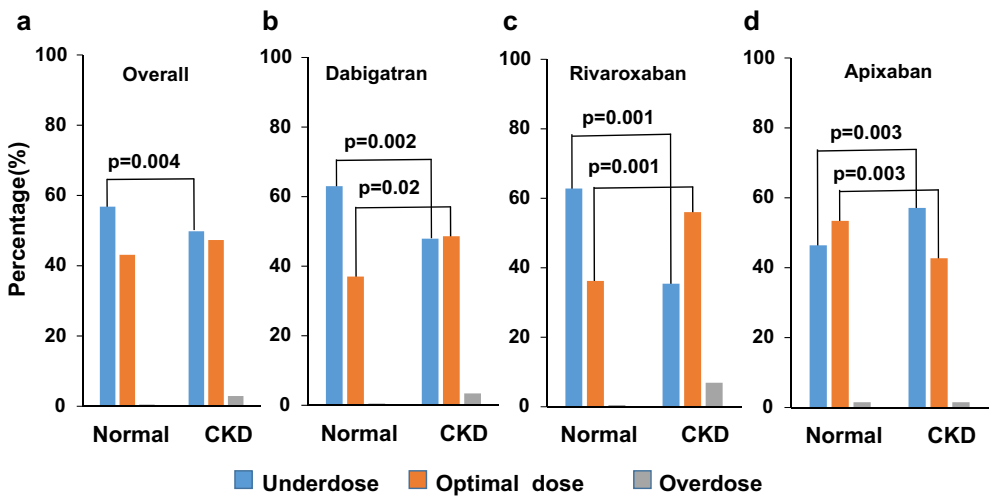

Fig. 3 Dosage of non-vitamin K oral anticoagulants (NOACs) in CKD patients. **a** Overall, **b** dabigatran, **c** rivaroxaban, and **d** apixaban. In the overall NOACs, the underdose rate was lower in CKD patients than in normal patients. CKD patients had a lower underdose rate and a higher optimal dose rate of dabigatran and rivaroxaban. However, CKD patients had a higher underdose rate and a lower optimal dose rate of apixaban. CKD, chronic kidney disease

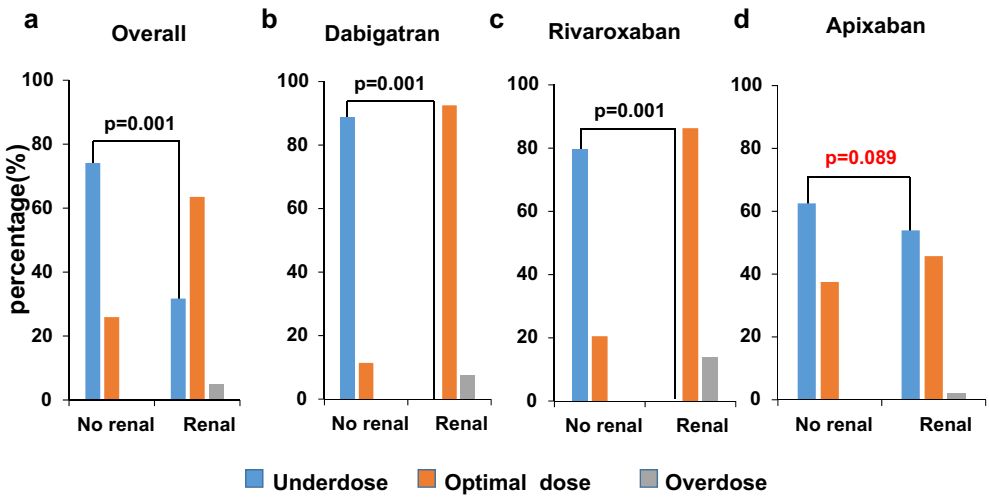

Fig. 4 Dosage of non-vitamin K oral anticoagulants in patients without and with renal dose reduction indication. **a** Overall, **b** dabigatran, **c** rivaroxaban, and **d** apixaban

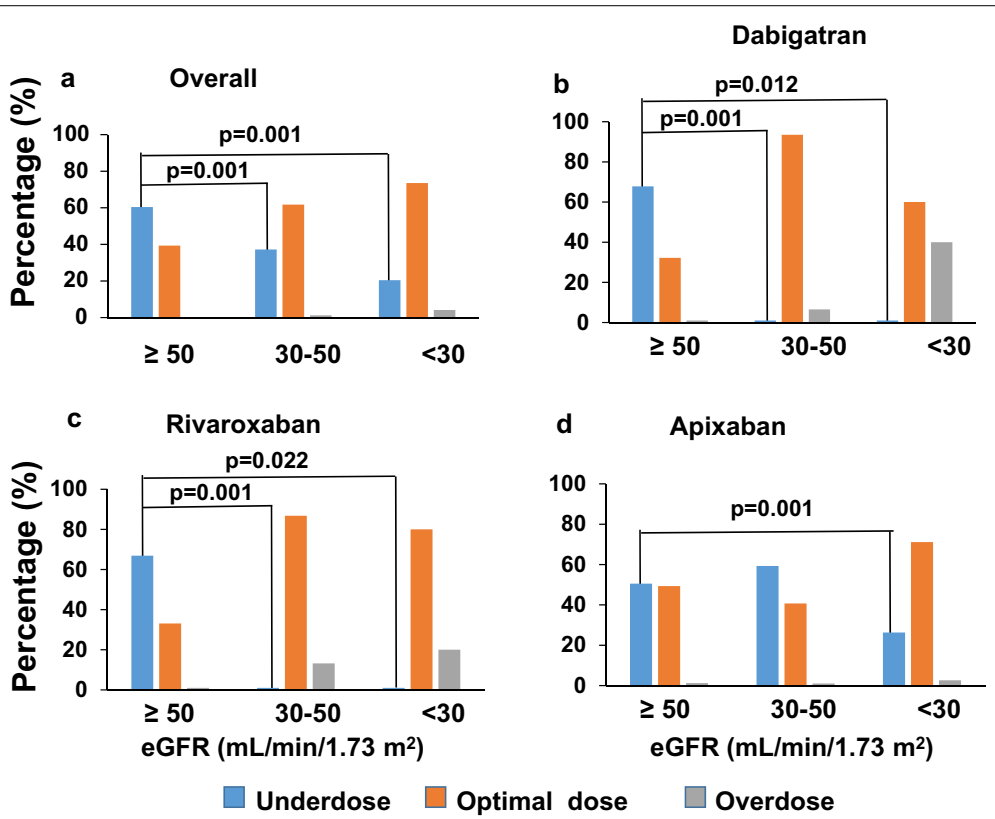

Fig. 5 Dosage of non-vitamin K oral anticoagulants (NOACs) according to eGFR in patients with chronic kidney disease. **a** Overall, **b** dabigatran, **c** rivaroxaban, **d** apixaban. In the overall NOACs, the dabigatran and rivaroxaban underdose rates were lower in patients with eGFR from 50 to 30 and < 30 mL min^{-1} 1.73 m^{-2} than in those with eGFR ≥ 50 mL min^{-1} 1.73 m^{-2}. eGFR, estimated glomerular filtration rate

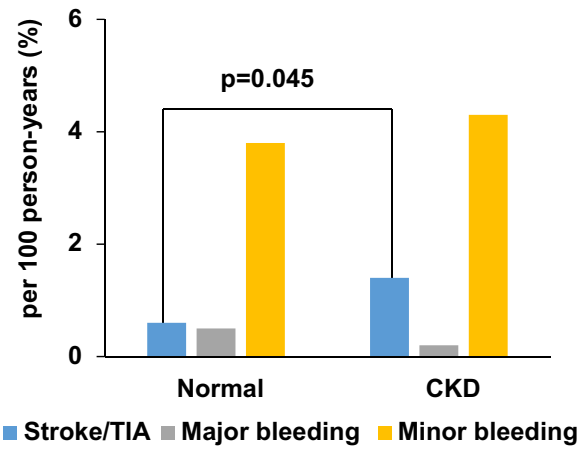

Fig. 6 Comparison of adverse outcome between normal and CKD patients. Stroke/TIA was significantly higher in CKD patients (1.4 vs. 0.6 per 100 person-years, $p = 0.045$). CKD, chronic kidney disease; TIA, transient ischemic attack

increased risk of stroke and embolic events and, irrespective of the anticoagulant administered, are also at an increased risk of bleeding events.

Dosage pattern of NOACs in CKD patients

Recent registry data suggest that inappropriate NOAC dosing is not uncommon [24, 25]. In this study, among patients with no-RIDR, the use of a reduced dose seemed to be more prevalent than what might be expected from extrapolation of clinical trial data [10]. However, in patients with RIDR, because of high usage of reduced dose, the rate of optimal dosing was increased dramatically. The use of a reduced dose was only a problem with apixaban. The high rates of optimal dosing of dabigatran and rivaroxaban in the CODE-AF registry are different from data in other registries. In ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), more than half (56%) of patients with severe kidney disease were not prescribed with reduced dosing, whereas 10% of patients with preserved renal function received lower dosing [24]. In the XANTUS (Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation) study, more than one-third of patients with creatinine clearance < 50 mL/min received the standard dose, whereas 15% of patients with creatinine clearance ≥ 50 mL/min received a reduced dose [25].

Surprisingly, < 10% of patients with RIDR did not receive a reduced dose. This percentage is much smaller than that reported in previous international studies [24–26]. Potential overdosing (i.e., use of standard dose NOACs in patients with severe renal impairment) was associated with a doubled risk of bleeding with no attendant reduction in the risk of stroke [26]. Although these registries provide some important insights, they are still selective (e.g., the enrolled patients were mostly treated by specialists) [27]; thus, they may have underestimated the extent of inappropriate dosing in everyday clinical practice. Furthermore, few data exist on how potential underdosing or overdosing affects the effectiveness or safety of these drugs.

Adverse event rate in CKD patients

Patients with AF and CKD have higher rates of stroke than those with normal renal function. One interesting finding was that aspirin was related to increased minor bleeding in CKD patients but not in normal patients. This finding supports the recent guideline in which the role of aspirin was reduced in stroke prevention in patients with AF [25].

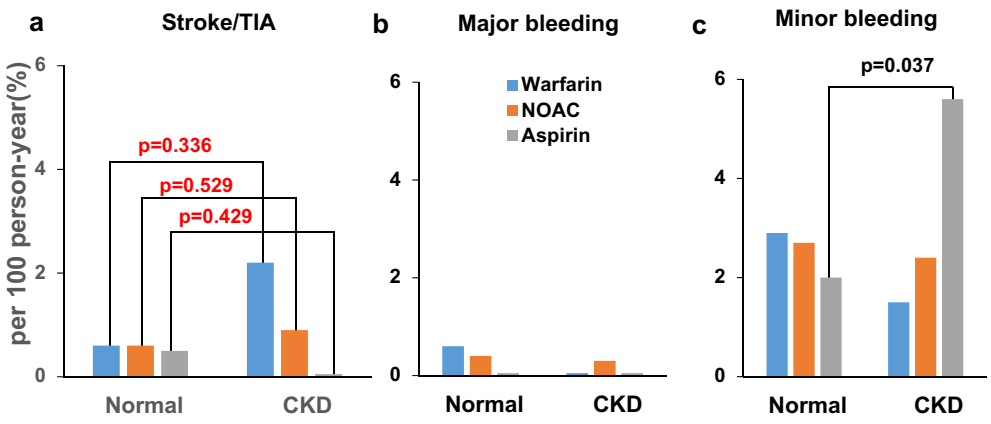

Fig. 7 Comparison of adverse outcome according to oral anticoagulation strategies between normal and CKD patients. Aspirin significantly increased minor bleeding in CKD patients compared with the normal group ($p = 0.037$). CKD, chronic kidney disease; TIA, transient ischemic attack

Potential underdosing (using reduced dose of NOACs in patients without severe renal impairment) was associated with a nearly fivefold increased risk of stroke in apixaban-treated patients. Recent studies suggest that the tendency to prescribe apixaban at a reduced dose comes at the cost of reduced effectiveness of stroke prevention. Interestingly, such patients seemed to have bleeding rates comparable to those receiving a standard dose. A similar underdosing effect was not seen in dabigatran- and rivaroxaban-treated patients. The use of rivaroxaban at a reduced dose was associated with a non-significant trend toward a lower stroke risk [26, 28]. However, in this study, the effect of dosing was not evaluated appropriately because of the small number of patients.

Study limitations

First, the average follow-up was short, which is commonly seen in OAC research involving "real-world" data. Several recent NOAC studies reported a mean follow-up of ≤ 6 months [29]. As this outcome is likely due to poor adherence to treatment in routine practice [30], it does not necessarily limit the generalizability of our results. Furthermore, a short follow-up does not limit the usefulness of our findings to inform practice because patients taking NOACs should be seen by physicians at least once or twice a year for the evaluation of kidney function and the appropriateness of dosing. Second, we only abstracted the most recent serum creatinine results before treatment initiation, which may not necessarily reflect the kidney function of patients during follow-up. However, for most patients, renal function was relatively stable. Third, this study is not a randomized trial study but an observational study looking at medication use. So there could be substantial selection biases. Furthermore, CKD and non-CKD patients have totally different baseline characteristics. So, we tried to apply the other statistical method such as propensity score matching, adjusted hazard ratio by using Cox proportional hazard model to strengthen the causality. However, the scale of data and the rate of outcome were very small. So, we could not apply the other statistical methods. Fourth, high stroke risk without anticoagulation ($n = 820$) were excluded from this study. Because this study sought to evaluate differences in anticoagulation strategy and outcome in atrial fibrillation patients with chronic kidney disease, we excluded that group. Lastly, the number of events and the event rates were low; therefore, the findings should be viewed as hypothesis generating and need to be confirmed by future studies.

Conclusion

CKD patients might have a high stroke risk and usage rate of NOACs. The underdose rate of NOACs decreased in CKD patients, except for apixaban. Aspirin significantly increased minor bleeding in CKD patients.

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None.

Authors' contributions
Y-JC analyzed the data and wrote the paper. BJ was involved in funding, conception of idea, writing paper, and critical review. J-SU, T-HK, M-JC, JML, JP, J-KP, K-WK, JS, JK, HWP, E-KC, J-BK, CK, and YSL acquired the data and critically reviewed. All authors read and approved the final manuscript.

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Availability of data and materials
None.

Ethical approval and consent to participate
This study was approved by the Institutional Review Board of Yonsei University Health System (4-2016-0105), which waived the need for informed consent.

Consent for publication
Get permission from all authors.

Competing interests
The authors declare that they have no competing interests.

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